Review Article

Innovative approaches to control hypertension: article review

Abstract:

Raised blood pressure is one of the top global risks for death and disability estimated to have caused over 10 million deaths. Improving the control of hypertension is a major global health care goal. Hypertension is also a major risk factor to most of heart diseases. Recent approaches to control hypertension require multidisciplinary efforts between patient, family, community and health team members. After a thorough literature review, the researcher found that approaches to control hypertension are still develops daily. It composed of pharmacological, non-pharmacological, surgical and technological approaches.

Introduction:

Cardiovascular disease (CVD) is the leading cause of mortality in the world, resulting in 17.3 million deaths annually, 1 Elevated blood pressure, a major risk factor for ischemic heart disease, heart failure, and stroke, is the leading global risk for mortality (Vedanthan et al., 2017).

According to WHO , hypertension has been identified as one of the most significant risk factors for morbidity and mortality worldwide and is responsible for the deaths of approximately nine million people annually (WHO., 2013). In the UK, the National Institute for Health and Care Excellence (NICE) defines high blood pressure (BP), also known as hypertension, as a clinic blood pressure of 140/90mmHg or higher confirmed by a subsequent ambulatory blood pressure monitoring daytime average (or home blood pressure monitoring average) of 135/ 85 mmHg or higher (Kitt et al., 2019).

High blood pressure does not just develop in older adults. Over 2.1 million people under 45 years old had high blood pressure in England in 2015. This is important because treating hypertension results in significant reductions in risk of

subsequent cardiovascular disease. Despite strong evidence for such treatment, studies suggest that many people remain suboptimally controlled. New approaches, including new technologies, are therefore needed to improve screening, detection and control of raised blood pressure in the community (Kitt et al., 2019).

Up growing incidence and poor disease control consider a burden on health care facilities. This health and economic burden nesseciate the need to address the problem by way of novel approaches (Vedanthan et al., 2017).

The innovative approaches to control hypertension are still progresses and develop till now. This review aimed to represent these innovative approaches and the rationale for each one.

Review:

Hypertension is an increase in systolic blood pressure above 130 mmHg and diastolic pressure above 80 mmHg (Carey& Whelton., 2017). Hypertension is a silent killer where symptoms can vary between individuals and are almost the same as symptoms of other diseases. Hypertension is an independent risk factor for cardiovascular disease, including coronary arteries, ischemic stroke, peripheral arterial disease and congestive heart failure (Strait & Lakatta., 2012). According to WHO 2013, it is estimated that in 2025 the prevalence of hypertension will increase to 1.5 billion people. Untreated hypertension, in the long run, will cause damage to the arteries. Complications of hypertension can occur in organs such as; heart, brain, kidney and eyes (Trtica Majnarić et al., 2019).

According to Forouzanfar et al., (2017) hypertension alone is responsible for 14%of deaths globally. The rate of hypertension has increased from 13,307/100,000 in 1990 to 20,525/ 100,000 in the year 2015. The prevalence of hypertension in adults ranges from 30 to 45% in different countries of the world (Mahmood et al., 2019)

Recent approaches to control hypertension require multidisciplinary efforts between patient, family, community and health team members. After a thorough literature review, the researcher found that approaches to control hypertension are still develops daily. It composed of pharmacological, non-pharmacological, surgical and technological approaches (Trtica Majnarić et al., 2019).

Innovative pharmacological approaches to control hypertension:

WHO is also working on its first hypertension clinical guideline, which is ready in 2021. Although guidelines can differ in certain features, such as the blood pressure threshold value required to start treatment or the target blood pressure for those on treatment, a clear consensus exists about the strong evidence for the effectiveness of four major classes of pharmacotherapies, including blockers of the renin–angiotensin–aldosterone system (RAAS), calcium channel blockers, β-blockers and thiazide or thiazide-like diuretics. Although specific indications exist for some of the pharmacological groups, such as β-blockers for patients with coronary artery disease or heart failure and RAAS blockers for patients with chronic kidney disease, a consensus has been established that all antihypertensive drugs have a similar effect on major cardiovascular outcomes, including mortality. Fixed-dose combination therapy, with two or more agents in a single pill, is a crucial component of the current medical management of hypertension. This approach has several advantages, including pharmacological (synergies of mechanisms of action and fewer adverse effects owing to lower doses) and practical (increasing adherence) aspects, and is currently recommended as initial therapy in most guidelines (Zhou et al., 2021; Williams et al., 2018).

According to Derington et al (2020) , between 2005 and 2008 and 2013 and 2016, a high proportion of US adults with hypertension were taking only one class of antihypertensive medication, even among those with uncontrolled BP. Use of ACEI or ARB monotherapy increased while the use of β-blocker monotherapy decreased. The current analysis suggests that a high proportion of uncontrolled BP among US adults with hypertension taking antihypertensive medication may be the result of an inadequate antihypertensive medication regimen. Therefore, initiatives to increase the use of dual- and triple-therapy antihypertensive medication regimens may present an opportunity to restore the upward trend in BP control rates in US adults.

Role of Interleukins in diagnosis and treatment of Arterial Hypertension:

Hypertension as a multifactorial pathology is one of the most important cardiovascular risk factors, affecting up to 30-40% of the general population. Complex immune responses are involved in the inflammatory mechanism of hypertension, with evidence pointing to increased inflammatory mediators even in prehypertensive patients. Increased vascular permeability, thrombogenesis, and

fibrosis, effects that are associated with sustained hypertension, could be attributed to chronic inflammation. Chronic inflammation triggers endothelial dysfunction via increased production of ROS through proinflammatory cytokines. Increased serum level of proinflammatory cytokines such as IL-1β, IL-6, IL-8, IL-17, IL-23, TGFβ, and TNFα in hypertensive patients has been associated with either increased blood pressure values and/or end-organ damage.Moreover, some cytokines (i.e., IL-6) seem to determine a hypertensive response to angiotensin II, regardless of blood pressure values. Understanding hypertension as an inflammatory-based pathology gives way to new therapeutic targets. As such, conventional cardiovascular drugs (statins, calcium channels blockers, and ACEIs/ARBs) have shown additional anti-inflammatory effects that could be linked to their blood pressure lowering properties. Moreover, anti-inflammatory drugs (mycophenolate mofetil) have been shown to decrease blood pressure in hypertensive patients or prevent its development in normotensive individuals. Further research is needed to evaluatewhether drugs targeting hypertensive-linked proinflammatory cytokines, such as monoclonal antibodies, could become a new therapeutic option in treating arterial hypertension (Tanase et al., 2019).

RNA Interference

RNA interference (RNAi) is a promising strategy for new hypertensive agents. RNAi is a naturally occurring regulatory mechanism to silence gene expression. RNAis are short RNAs that activate ribonucleases to target homologous mRNA resulting in the silencing of a specific gene (Ballicora et al., 2003). RNAi is an important tool for researchers to learn about the function of a gene but also for therapeutic intervention—to target diseases that may result from undesirable activity of a gene. Already, RNAi has been used successfully for cardiovascular research and is being evaluated for human therapy. For example, RNAi has been used to target PCSK9 (proprotein convertase subtilisin/kexin type 9), a recently identified but well-validated target for low-density lipoprotein cholesterol– lowering therapy. PCSK9, an enzyme expressed and secreted into the bloodstream predominantly by the liver, plays an important role in cholesterol metabolism and also seems to modulate hypertension (Melendez et al., 2017). Of note, *PCSK9* loss-of-function mutations are associated with low circulating low-density lipoprotein cholesterol levels and diminished cardiovascular risk with no apparent negative health consequences. In phase 2 clinical trial, RNAi has been shown to significantly reduce levels of PCSK9 and low-density

lipoprotein cholesterol in humans for 6 months of follow-up. This is proof of concept that RNAi can be an effective modality for long-term treatment of cardiovascular disease (Dzau & Balatbat., 2019).

Angiotensinogen:

As for hypertension, example of an important therapeutic target is angiotensinogen, the sole substrate of the reninangiotensin system. Studies have demonstrated a relationship between angiotensinogen and hypertension, suggesting that decreased production of angiotensinogen may be a useful target for novel hypertension drugs. One can envision an RNAi approach targeting angiotensinogen in the liver, the main production site of circulating angiotensinogen. Indeed, researchers have already shown that siRNA can be used to reduce angiotensinogen production in the liver of rats, which resulted in decreased plasma angiotensinogen and decreased blood pressure in both hypertensive and normotensive rats. These results were sustained suggesting that this treatment would not need to be administered daily.43 However, further research is needed to examine efficacy and safety for humans (Dzau & Balatbat., 2019).

Gene Editing—Somatic Gene Editing of PCSK9

Another promising strategy is the use of genome editing to target genes for human hypertension therapy. Similar to the use of RNAi, researchers have already demonstrated that CRISPRCas9 genome editing technology can be used to effectively target mouse PCSK9 in vivo as well as in authentic human hepatocytes in vivo in a liver-humanized mouse model (Wang et al., 2016). In addition, researchers editing monkeys' genomes in their livers reduced the animals' blood cholesterol levels. Wang et al (2018) showed that single infusions in nonhuman primates of adenoassociated virus vector expressing an engineered meganuclease targeting PCSK9 results in dose-dependent disruption of PCSK9 in liver, as well as a stable reduction in circulating PCSK9 and serum cholesterol. PCSK9 levels dropped by as much as 84% and low-density lipoprotein levels dipped as much as 60% in treated monkeys. These results suggest that PCSK9-targeting genome-editing therapies could be effective in humans. However, further research will be needed to prevent off-target effects, unwanted immune effects, and validate the efficacy of the technology in clinical trials. In the future, genome editing (using CRISPR-Cas9) holds promise for curing genetic

hypertension, and in targeting angiotensinogen and other targets, resulting in possible long term control of essential hypertension (Dzau & Balatbat., 2019).

Innovative Non pharmacological approaches to control hypertension:

Unhealthy eating habits, decreased physical activity, obesity, smoking, and alcohol consumption are the key factors for development of hypertension. Proper management of hypertension is necessary in order to prevent its complications and to improve the quality of life of the patient. Hypertension management involves both pharmacological and non-pharmacological interventions for effective control. Despite the availability of very effective medications, the blood pressure cannot be controlled in about 70% of patients who receive only pharmacological treatment for hypertension (Selçuk et al., 2017). The non-pharmacological interventions can be utilized alone before starting the pharmacological therapy or in combination after (Mahmood et al., 2019; Mercer et al., 2020).

Dietary modifications:

Dietary habits are directly linked to hypertension. The research studies proved that a diet rich in fiber and dairy products, low in Na+, rich inK+ and Mg+2, and high in polyunsaturated fatty acids is beneficial for the prevention and management of hypertension. Current clinical guidelines recommend the lifestyle modifications, as an initial treatment in prehypertension stage and in combination with pharmacological treatments in all other stages of hypertension for better management of hypertension. Despite of all the positive findings for the beneficial effects of dietary modifications, the healthcare practitioners are still not clear as which dietary approach to recommend. It has been observed that individuals on vegetarian diet are less likely to develop hypertension and other cardiovascular diseases. The Dietary Approach to Stop Hypertension (DASH) and Traditional Mediterranean Diet^ are the highly recommended dietary approaches for the prevention and management of hypertension (Mahmood et al., 2019; Azadbakht et al., 2011).

The DASH diet: DASH diet was designed for the prevention and effective management of hypertension. It is now considered as diet of choice for the prevention and treatment of hypertension. The effectiveness of DASH diet has been established

through DASH trials conducted in different parts of the world. It composed of low sodium and low fat diet. While the main features of Mediterranean diet are (1) increase intake of fruits, vegetables, and pulses, (2) high consumption of monounsaturated fatty acids and polyunsaturated fatty acids, (3) less consumption of red meat, and (4) restricted intake of alcohol (Mahmood et al., 2019; Saneei et al., 2014).

Sodium restriction: Sodium plays an important role in pathophysiology of hypertension. A high salt diet leads to profibrotic changes in vascular smooth muscles through induction of collagen synthesis. This collagen deposition in blood vessels leads to arterial stiffness. Daily Na+ intake of 2400 mg/24 h is considered as normal/beneficial. Whereas further reduction to 1500 mg/ 24 h recommended in the persons who are at increased risk of hypertension or stroke (Mahmood et al., 2019; Van Horn., 2015).

Potassium and magnesium supplementation:

Potassium intake has an inverse correlation with hypertension. Recent research showed that K+ consumption has an important role in salt-sensitive hypertension especially in black population. Salt loading increases mean arterial blood pressure by 6.8 mmHg in African/Black population vs 1.9 mmHg in white population when given low K+ diet. This hypertensive effect was reduced by 4.9/3.3 mmHg in black population vs 2.5/1.9 mmHg in white population when given high K+ diet to the participants, i.e., 70mmol.day. Like potassium, magnesium also has an inverse correlation with hypertension. Mg+2 is found rich in fruits and vegetables that are studied for beneficial effects against hypertension. A meta-analysis of 34 trials involving 2028 normotensive and hypertensive participants showed a positive effect for Mg+2 intake (368 mg/day) for 3 months in lowering blood pressure to 2.0 mmHg SBP and 1.78 mmHg DBP (Mahmood et al., 2019; Tang et al., 2016).

Antihypertensive Effects of Antioxidants

Together with taking into account the role of ROS in the pathophysiology of hypertension, the view of the potential effects of antioxidants as pharmacological agents leading to counteract blood pressure elevation has been suggested from various sources. Thus, antioxidant-rich diets have resulted in lowering blood pressure in hypertensive subjects, and supplements of antioxidant vitamins reduced both systolic and diastolic blood pressure in patients with essential hypertension. Naturally occurring antioxidants, such as wine polyphenols have also been considered as

positive modulators of endogenous antioxidant defense systems (Rodrigo et al., 2012). Several preclinical studies and clinical trials have indicated that antioxidant therapy is important for the management of hypertension, using antioxidant compounds such as ascorbic acid (vitamin C), alpha-tocopherol (vitamin E) and polyphenols, and some antihypertensive drugs are now in clinical use (e.g., ACEIs, ARBs, novel B-blockers, dihydropyridine CCBs), which have anti-oxidative pleiotropic effects (Rodrigo et al., 2021).

Minimizing alcohol intake:

Reduction of alcohol intake is one of the recommendations in JNC-8 guidelines. Excess alcohol consumption is responsible for 5– 30% of all hypertension cases. Alcohol intake is directly correlated with elevated blood pressure. The reduction in weekly alcohol from 452 to 64 ml was found to be associated with 5/3 mmHg reduction in blood pressure in 3 weeks (Mahmood et al., 2019). A meta-analysis of 15 randomized control trials involving 2234 individuals revealed that alcohol reduction was associated with 3.3/2.04 mmHg reduction in blood pressure (Xin et al., 2001).

Body weight and exercise:

Physical activity is the major lifestyle modification for the management of hypertension. There are a number of studies that support the relationship between physical activity and hypertension. Individuals with a higher fitness level have lesser chances to develop hypertension (Faselis et al., 2021). Meta-analysis of 28 randomized controlled trials involving 1012 individuals divided in 33 subgroups revealed that dynamic resistance training exercise resulted in reduction of both systolic and diastolic blood pressure by 2.6/3.11 mmHg respectively as compared to a non-training control group; similarly, isometric handgrip training resulted in 11.8/5.8 mmHg reduction in both systolic and diastolic blood pressure as compared to the non-training control group (Cornelissen et al., 2011).

Reduced physiological stress and anxiety:

Transient elevation in blood pressure occurs in response to physiological stress and anxiety. The episodes of stress and anxiety may lead to persistently elevated blood pressure. There are numerous studies that link depression with cardiovascular diseases. Stressful events like sorrow, disappointment, disasters, and fear are positively associated with hypertension. Stress and anxiety lead to enhanced sympathetic activity through the release of epinephrine into the blood, resulting in

elevated blood pressure. Secondly, stress results in an increase in cortisol release in the body leading to hypertension (Grassi., 2009; Brettler & Sharman., 2023).

Warm water foot bath therapy

One alternative therapy for non-pharmacological management to reduce blood pressure is to do a combination of warm water foot bath therapy and progressive muscle relaxation. Scientifically warm water has a physiological impact on the body which is smooth blood circulation, stabilizing blood flow and heart work as well as loading factors in the water which will strengthen the muscles and ligaments that affect the joints of the body. Soaking warm water is beneficial for vasodilation in blood flow so that it can reduce blood pressure (Fadlilah et al., 2020).

Progressive muscle relaxation technique

Progressive muscle relaxation is stretching and releasing muscle groups that will produce different sensations. The benefits of progressive muscle relaxation are to reduce physical stress, decrease pulse, blood pressure and breathing without any side effects. The reason for choosing a combination of a warm foot soak and progressive muscle relaxation is because this procedure is more practical, easy, inexpensive, affordable. This therapy can be applied to hypertensive patients and has no side effects (Fadlilah et al., 2020).

Innovative surgical approaches to control hypertension:

Resistant hypertension is defined as uncontrolled blood pressure despite the use of optimal doses of three antihypertensive agents, of which one is a diuretic. It has been shown that a majority of patients with resistant hypertension and no identifiable secondary causes have activated sympathetic nervous system and increased sympathetic outflow. Surgical sympathectomy was driven to total obscurity primarily due to serious adverse effects. It should be noted, however, that sympathectomy was the first attempt to effectively confront malignant hypertension and its consequences through an interventional approach. Indeed several studies have shown sympathectomy to be very effective in reducing blood pressure, and results were maintained in the long term (Calhoun et al., 2008).

Selective renal sympathetic denervation (RSD)

Selective renal sympathetic denervation (RSD) is the latest and perhaps the most interesting approach used recently in an attempt to interrupt the influence of the sympathetic nervous system on the kidney and systemic hemodynamics. Renal sympathetic ablation was achieved using a radiofrequency ablation catheter inserted through the femoral artery and selectively engaging the renal artery bilaterally (Papademetriou et al., 2011).

Baroreceptor stimulation

Baroreceptor stimulation is achieved through this pulse generator implanted subcutaneously (much like a pacemaker), which is connected to two leads rubbed around the carotid bulbs. The two early studies that include about 110 patients demonstrated significant efficacy of the device with up to 30/18mmHg reduction in blood pressure, which can be maintained long term. A larger pivotal study, which included a blinded arm, recently completed recruitment of 300 patients. The study is still in progress, and results have not been announced (Courand et al., 2014; Papademetriou et al., 2011).

Role of mobile technology in controlling hypertension:

Some of the challenges in treating and managing chronic conditions are suboptimal adherence to management guidelines by the physicians (Jindal et al., 2018), lack of regular patient monitoring and undiagnosed comorbidities such as anxiety, depression, and alcohol use disorders which can contribute to failure to follow treatment plans. Mobile health (mHealth) technologies are being advocated to strengthen the health system, and systematic reviews have shown that an mHealth-based Clinical Decision Support System (CDSS) improves preventive care and the physician's clinical decision quality in hypertension and diabetes management although the evidence on their effects on cardiovascular outcomes is limited (Venkataraman et al., 2009).

Considering the potential of mobile technology to address some of the challenges in chronic disease management, we sought to develop a tablet-computer enabled mHealth intervention (called mWellcare) with the goal of integrated management of hypertension, diabetes, and other comorbid conditions at the primary health care level in India. This intervention is intended to be used by general health care providers (nurses/ physicians) in primary care settings. The aim of this paper is to

describe the steps and processes in the development and design of themWellcare intervention (Berntson et al., 2015; Anchala et al., 2021).

Role of Telemedicine in hypertension control:

Tele-monitoring is a particular application of telemedicine—the transfer of data remotely which in this case consists of automatic data transmission of BP readings. It can also be combined with the transfer of other parameters such as heart rate, oxygen saturations, and pacemaker/defibrillator data from the patient's home or workplace to a professional healthcare environment such as a primary care clinic/surgery or the hospital. Several tele-monitoring systems are available which differ in their modality of data collection, transmission, and reporting and by the presence/absence of additional features such as reminders for BP measurement to be performed or medication reminders (Kitt et al., 2019; Omboni & Ferrari., 2015).

Role of Virtual clinics/visits:

'Virtual clinics/visits' provide a system-level option for the use of such technology and comprise structured asynchronous online interactions between a patient and a clinician to extend medical care beyond the initial office visit. A study by Levine et al. in 2018 showed that for primary care patients managed for hypertension with a virtual visit vs. a real-life in-person visit, there was no significant adjusted difference in systolic blood pressure control, number of specialist visits, emergency department presentations, or inpatient admissions (Kitt et al., 2019; Levine et al., 2018).

Artificial intelligence and controlling hypertension:

There is a need for data modeling, robust statistical tools, and a more personalized approach to study patients with hypertension as well as those with poorly controlled hypertension. Thus, novel study designs to be used in clinical trials can improve the detection, evaluation, treatment and prevention of hypertension, as well as improve adherence. Artificial intelligence (AI) is the ability of a computer to simulate human thought processes (i.e., decision-making) based on substantial amounts of data, sophisticated algorithms, and high computational power. AI can be classified into several subfields such as machine learning (ML), deep learning (DL), or cognitive computing. To generate predictions, ML can rapidly assess multiple texts, social

media, vital signs, electrocardiogram (EKG), echocardiography, and data capturing by wearable technology simultaneously. AI can formalize very complex decisions and predictive analysis, leading to personalized medicine. In advancement of DL and pattern recognition, particularly EKG and echocardiographic video, this could potentially transform hypertension diagnosis with early detection and preemptive management. In addition, an integrated combination of genetics and environmental factors could underpin the mechanism of poorly controlled hypertension. In this review, we discuss the potentials of AI for predicting the risk of developing hypertension, the possible AI applications for the treatment of hypertensive patients, and future direction of clinical trials of hypertension guided by AI towards personalized medicine (Krittanawong et al., 2018; Matsuoka et al., 2020).

Conclusion:

Hypertension is one of the most pressing public health challenges. It is recognized as the biggest contributor to the global burden of disease. The global burden of hypertension has been growing over time, largely driven by population growth, changes in lifestyle, and aging. Alarmingly, hypertension is controlled in less than a fifth of patients worldwide. Furthermore, there are vast global disparities in hypertension awareness, treatment, and control. Detecting hypertension early and taking measures to control it may be a cost-effective way to reduce the hypertension-related disease burden. Hypertension is often referred to as the silent killer because there are often no symptoms or warning signs. There are many ways to control hypertension. Most of them become traditional and less effective due to increased pathophysiological causes of hypertension. This variety inspires scientists to innovate methods for hypertension control that ranges between pharmacological, non-pharmacological, surgical and technology based approaches.

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